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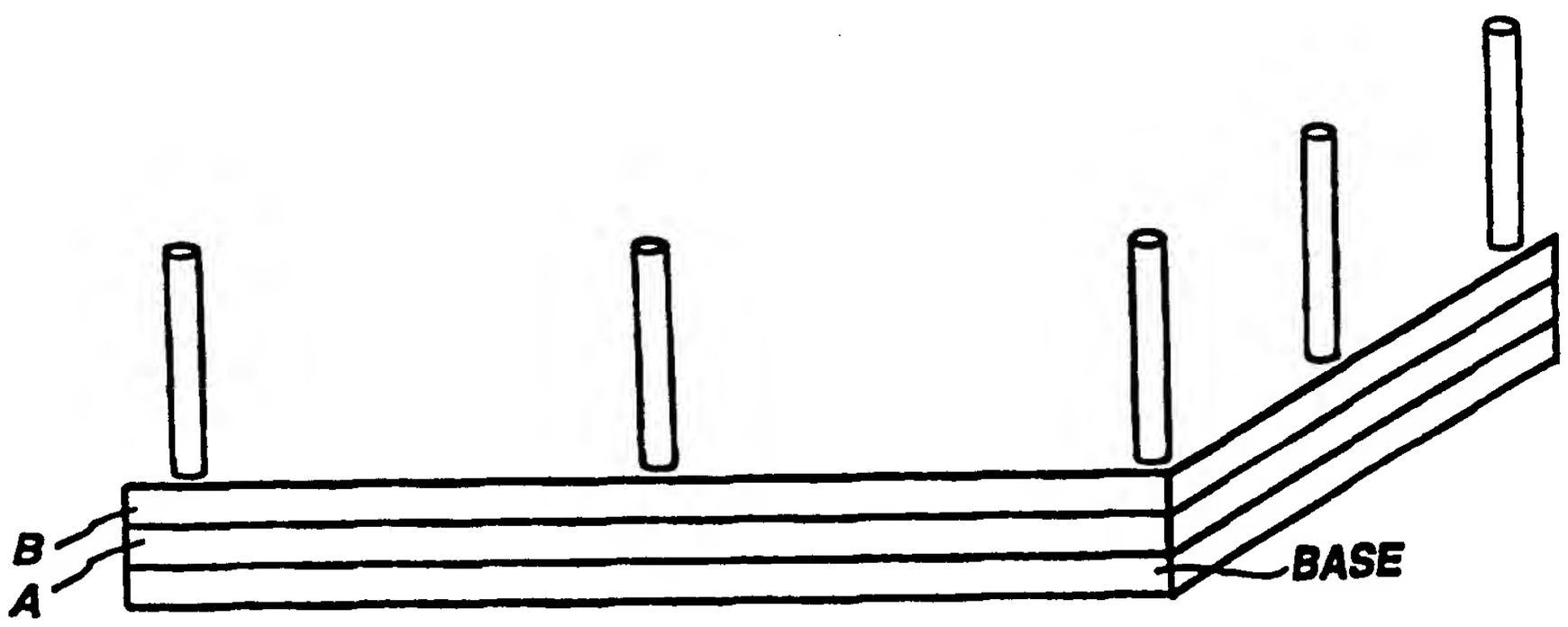

(57) Abstract

This invention features methods and devices for rapidly, efficiently and conveniently synthesizing combinatorial libraries of chemical compounds. The present invention provides an efficient method for synthesizing N^2 or N^3 compounds. Specifically, a two-dimensional or three-dimensional conduit synthesis device is provided.

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DESCRIPTION

Multidimensional Conduit Combinatorial Library Synthesis Device

Background of the Invention

This invention relates to combinatorial library synthesis devices used to generate combinatorial libraries of chemical compounds.

The generation of combinatorial libraries of chemical compounds utilizing standard laboratory techniques of repetitively, separately reacting and mixing chemical compounds composing combinatorial libraries has been described in the art. The initial report of rapid concurrent solid phase synthesis by Geysen and co-workers, Geysen, H.M.; Meleon, R.H.; Barteling, S.J., 81 *Proc. Natl. Acad. Sci. USA* 3998, 1984, described the construction of multi-amino acid peptide libraries. Houghten et al., 354 *Nature* 84, 1991 and WO 92/09300 (PCT/US91/08694), describe the generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery. These libraries are composed of mixtures of free peptides which form a heterogenous library. Lam et al., 354 *Nature* 82, 1991, and WO 92/00091 (PCT/US91/04666) and Houghten et al., 354 *Nature* 84, 1991 and WO 92/09300 (PCT/US91/08694), herein, describe systematic synthesis and screening of peptide and other libraries of defined structure. The method used is based on a one bead one peptide approach in which a large peptide library consisting of millions of beads are screened. Each bead contains a single peptide. The authors state:

"It is clearly not enough to use a random mixture of activated amino acids in a peptide synthesis protocol, because the widely different coupling rates of different amino acids will lead to unequal representation and because each bead will contain a mixture of different peptides. Our solution was to use a 'split synthesis'

approach. The first cycle consisted of distributing a pool of resin beads into separate reaction vessels each with a single amino acid, allowing the coupling reactions to go to completion, and then repooling the beads. The cycle was repeated several times to extend the peptide chain. In this fashion, each bead should contain only a single peptide species."

The library of beads was screened by a staining procedure and stained beads visualized using a microscope, and removed. The structure of the peptide is obtained by a chemical analysis of the material on the single bead. Lam et al. indicate:

"Additionally, our approach has far greater potential for applying the richness of well-established peptide chemistry to synthesize libraries incorporated D-amino acids or unnatural amino acids as well as specific secondary structures including cyclic peptides. All of this can be accomplished without need to keep records of the synthetic products as our interest is focused just on those peptides which provide a strong interaction signal with the acceptor."

Dower et al., WO 91/19818 (PCT/US91/04384) describes peptide libraries expressed as fusion proteins of bacteriophage coat proteins.

Dower et al., WO 93/06121 (PCT/US92/07815) describes a method for synthesizing random oligomers and the use of identification tags to identify oligomers with desired properties.

Huebner, United States Patent 5,182,366 describes the controlled synthesis of peptide mixtures using mixed resins. However, none of these references focus on the use of a device which allows for the rapid, efficient and convenient synthesis of combinatorial libraries.

Ellman, United States Patent 5,288,514 describes the solid phase and combinatorial synthesis of benzodiazepine compounds on a solid support. Ellman also discloses the use of a 96 pin block in which the pins act as a solid

support for the sequential coupling of benzodiazepines. Each pin of the 96 pin block is configured to be lowered into a series of 96-well microtiter reaction plates.

Winkler et al., WO93/09668 (PCT/US92/10183) discloses a method and device for forming large arrays of polymers on a substrate. The method and device relies on the use of thousands of channels to deliver compounds to a substrate on a surface and thereby generate molecular diversity. Photolithographic methods as are known in the art are also set forth in Winkler et al.

The generation of diverse collections of molecules in sizable amounts utilizing rapid, efficient and convenient methods requires the development of devices to meet this need.

Summary of the Invention

This invention features methods and devices for rapidly, efficiently and conveniently synthesizing combinatorial libraries of chemical compounds.

A "combinatorial library" is a collection of compounds in which the compounds comprising the collection are composed of one or more types of subunits. The subunits may be selected from natural or unnatural moieties, including dienes, dienophiles, amino acids, nucleotides, sugars, lipids, and carbohydrates. The compounds of the combinatorial library differ in one or more ways with respect to the number, order, type or types of or modifications made to one or more of the subunits comprising the compounds. Alternatively, a combinatorial library may refer to a collection of "core molecules" which vary as to the number, type or position of R or functional groups they contain and/or identity of molecules composing the core molecule, for example, a diene and/or dienophile which react to form the core molecule. The collection of compounds is generated in a systematic way, for example by the method of Lam or Houghten, however, any method of systematically generating a collection of subunits

differing from each other in one or more of the ways set forth above is a combinatorial library.

In one embodiment of the invention a three-dimensional conduit synthesis device is provided. The invention comprises a first array of cells that is aligned along one or more axes, a second array of cells aligned along one or more axes, and a means for communication between the first and second arrays of cells and to and from each cell in the arrays. The invention is useful for the efficient parallel synthesis of multi-milligram quantities of compounds.

A cell is a compartment which can contain reactants and solvents utilized in the synthesis of compounds comprising a combinatorial library. The cell may have a porous disk bottom and an open top. The sides of the cell may be flanged. The cells may have a shape which allows one cell to be securely stacked on top of another by nesting the bottom of the upper cell into the open top of the bottom cell. The cell bottom may be any shape but is preferably cylindrical.

The cells are arranged in arrays. An array is a set of two or more cells. The present invention may have at least two arrays of cells. The array of cells can be arranged in any geometric orientation, including planes, squares, cubes, spheres. The arrays may be connected by a means for communication among the arrays. A means for communication may also connect the cells within an array, and may connect certain cells from separate arrays. A preferred means of communication are conduits.

The present invention also includes a means for moving substrates and reagents along the means for communication. Such means for moving substrates and reagents may include pressure differential, gravitational force, mechanical force and electromagnetic force.

A preferred embodiment of the present invention features the arrays of cells on a planar surface, such as a tray. The cells may be regularly arranged in the tray.

The trays may be stacked such that each cell in a particular tray fits securely into a cell in the tray that is immediately below the particular tray. The upper most tray of the stacked tray may have conduits or channels which allow reagent and substrates to enter the stack of trays. The lower most tray may have conduits or channels that allow waste to be evacuated from the stack of trays. A system of conduits may allow reagents to flow among trays and among cells. Each tray may also contain one or more fiducial holes which allow the trays to be strung together and which serve as spatial reference points.

In another embodiment of the present invention a two-dimensional conduit synthesis device is provided. A "two-dimensional conduit synthesis device" has a first array of cells aligned along a first axis and a second array of cells aligned along a second axis, wherein the first and second axes may be perpendicular to each other. A cell is a compartment which can contain reactants and solvents utilized in the synthesis of compounds comprising a combinatorial library.

In a preferred embodiment the two-dimensional conduit synthesis device is used to synthesize a dimer library of n x n dimers, wherein n corresponds to the number of cells in an array and n may vary from 2 to 100. The dimers are comprised of subunits which may be selected from but is not limited to the following chemical moieties, amino acids and amino acid analogs, nucleic acids and nucleic acid analogs, carbohydrates and carbohydrated analogs, alkyl, alkenyl, alkynyl, alkoxy, aryl, alkylaryl, amide, thioamide, ester, amine, ether, thioether.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkyl group may be substituted or unsubstituted. When

substituted the substituted group(s) may be, hydroxyl, cyano, alkoxy, =O, =S, NO_2, $N(CH_3)_2$, amino, or SH.

An "alkenyl" group refers to an unsaturated hydrocarbon group containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. More preferably it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) may be, hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, $N(CH_3)_2$, amino, or SH.

An "alkynyl" group refers to an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or unsubstituted. When substituted the substituted group(s) may be, hydroxyl, cyano, alkoxy, =O, =S, NO_2, $N(CH_3)_2$, amino or SH.

An "alkoxy" group refers to an "-O-alkyl" group, where "alkyl" is defined as described above.

An "aryl" group refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, NO_2, amine, thioether, cyano, alkoxy, alkyl, and amino groups.

An "alkylaryl group" refers to an alkyl (as described above), covalently joined to an aryl group (as described above).

"Carbocyclic aryl groups" are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted.

"Heterocyclic aryl groups" are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the

remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted.

An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alklyaryl or hydrogen.

A "thioamide" refers to -C(S)-NH-R, where R is either alkyl, aryl, alklyaryl or hydrogen.

An "ester" refers to an -C(O)-OR', where R' is either alkyl, aryl, or alklyaryl.

An "amine" refers to a -N(R'')R''', where R'' and R''', is independently either hydrogen, alkyl, aryl, or alklyaryl, provided that R'' and R''' are not both hydrogen.

An "ether" refers to R-O-R, where R is either alkyl, aryl, or alkylaryl.

A "thioether" refers to R-S-R, where R is either alkyl, aryl, or alkylaryl.

The two-dimensional conduit synthesis device may be utilized in conjunction with s split synthesis, deconvolution method of generating a combinatorial library. Briefly, the standard method is performed as follows. In one example, the method involves a first step of attaching ten different subunits A, B, C . . . J, to a solid support in ten separate vessels or columns. In the second step, a portion or aliquot of the material synthesized at the first step is retained as separate columns, while the remainder (which is still attached to individual solid supports) is mixed or pooled, divided into ten new different columns, and ten further parallel syntheses carried out to provide the dimer XA^1, XB^1, XC^1 . . . XJ^1, where X is any one of the original A-J, and A^1, B^1, C^1 . . . J^1 are ten different subunits which may be the same or different from A-J. Of course, fewer or more than ten syntheses can be used in this second step. In the third step, a portion of the newly synthesized material of

step two is again retained in separate columns, and the remainder mixed and divided into ten further columns so that the synthetic procedure can be repeated until the whole length of the desired polysubunit is synthesized. In this way a series of vessels is formed at each step, differing from those in prior steps by the presence of an extra subunit.

The final ten columns in the above example (each having a variety of different polysubunits with a known subunit at their terminus) can be assayed using any standard assay format. That is, each of the ten mixtures is assayed to determine which mixture contains one or more active compounds. The column which is found to contain an active compound identifies the subunit required at the polysubunit terminus to be active in the assay. For example, the column containing polysubunits of sequence $XXXXJ^1$ may be active in the assay. This indicates that J^1 is required at the terminus of a polysubunit in this assay. This subunit is now bonded to each of the columns retained in the previous synthetic step (in the example, the columns XXXA, XXXB, . . . XXXJ). These ten newly synthesized series of compounds can then be assayed and the process repeated until the final polysubunit sequence is known.

The advantage of utilizing the two-dimensional conduit synthesis method in conjunction with the standard method is as follows. Upon determination of the last two subunits of a compound of a library, by deconvolution as above, the appropriate dimer from the appropriate cell of the two-dimensional conduit synthesis device may be added to a combinatorial library generated by the standard split synthesis method allowing more rapid and convenient deconvolution of those libraries. For example, if the last two subunits of a molecule are determined to be n1 and n5 then dimer n1/n5 generated by the two-dimensional conduit synthesis device may be used to deconvolute the

library, as opposed to first adding n1 and then adding n5 to the preceding subunit stage of the library.

An advantage of the present invention is that it allows for efficient synthesis and manipulation of combinatorial libraries of molecules.

Another advantage of the present invention is that it allows synthesis of a great diversity of unique compounds in unlimited amounts.

An additional advantage of the present invention is that each individual compound is synthesized in its own cell. The synthesized compounds can then be readily identified by its cell's position.

A further advantage of the present invention is that it allows three-dimensional synthesis, which adds an additional dimension for combinatorial synthesis.

Other and further objects, features and advantages will be apparent from the following description of the presently preferred embodiments of the invention.

Brief Description of the Figures

The figures will first briefly be described.

Figure 1 shows a top perspective of a tray of cells, the edges of the tray having fiducial holes.

Figure 2 shows a side view of stacked trays with guides threaded through the fiducial holes.

Figure 3A shows a cross-section of two stacked trays, illustrating the nesting of one cell into another.

Figure 3B shows a cross-section of a cell.

Figure 4A is a top view of the bottom tray in a stack of trays, illustrating a possible layout of conduits or channels that allow the movement of reagents and substrates among the cells and the evacuation of reagents and substrates from the cells and trays.

Figure 4B is a top view of the top tray in a stack of trays, illustrating a possible layout of conduits or channels that allow the entry of reagents and substrates into the stack of trays and into the cells of each tray.

Figure 5A is a top view of the top tray or top layer in a stack of trays, illustrating a possible layout of conduits or channels.

Figure 5B is a top view of the bottom tray or bottom layer in a stack of trays, illustrating a possible layout of conduits or channels.

Detailed Description of the Invention

The present invention is an efficient method for synthesizing N^2 or N^3 compounds. Other compounds can be made by subunit extension, by sequential operation, or parallel synthesis in addition to the compounds generated by the invention. The method of the present invention may provide 0.1 mmoles of each compound. This amount is equivalent to 50 mg for a compound of molecular weight 500. The device is also simple and compact.

The invention allows for parallel synthesis on a larger scale and with higher yields than those available by conventional methods. The invention also allows synthesis of combinatorial libraries with greater diversity and in large quantities. The invention also allows for easy identification and manipulation of the synthesized compounds.

Another advantage of the present invention is that it allows different chemical reagents to be routed to different cells. The invention also allows different cells to have different temperature conditions if the cells are insulated from each other.

The three-dimensional conduit synthesis of the present invention is particularly useful for creating and identifying pharmacologically active and medicinally useful molecules and sets of molecules. The invention allows the rapid, efficient and convenient generation and screening of sets of pharmacologically active molecules. Once a pharmacologically active molecule or set of molecules has been identified, the present invention may then again be used to optimize the active molecule or set of

molecules by making slight variations in the molecule or set of molecules.

The present invention is also useful for the rapid generation of a large, highly diversified library of compounds. The high diversity of the library allows rapid and accurate experiments and assays to be performed on a large diversity of compounds.

The present invention is also useful for the automated synthesis and automated screening of a large range of potentially biologically active compounds.

To assist in understanding the present invention, the synthesis of a 1000 compound combinatorial library using the present invention is described below. The following example relating to the present invention should not, of course, be construed as specifically limiting the invention, and such variations of the invention, now known or later developed, which would be within the purview of one skilled in this art, are to be considered to fall within the scope of this invention as claimed below.

Example

Synthesis of 1000 Compound Combinatorial Library By Three-Dimensional Conduit Synthesis

Each compound is synthesized in its own cell. If N, the number of cells in an array, equals 10 then 10^3 or 1000 cells will be needed. The subunits may be synthesized on a solid support for example beads. One 100 μ diameter bead carries approximately 100 pmoles of a compound. Therefore, to make 100 μmoles of any compound 10^6 beads will be required. The volume of each bead is 10^6 μ^3. 10^6 beads occupy 10^{12} femtoliters (1 μ^3 is 1 femtoliter), requiring *i.e.*, 1 milliter.

These beads may be accommodated in a cylindrical well, or cell, that is approximately, 1 cm in diameter and 1 cm deep. The cell may be a cylindrical well having a female flange at the top of the cell and a male flange at the bottom of the cell and a porous disk at the base of the

cell. If teflon is used as the porous disc material of the present invention, for example, then the disk could have 50 μ holes. The flanges may seal fairly tightly. The flanges may be straight and seal fairly tightly.

The male and female flanges could be separate layers bonded to the main tray. It may also be possible to have seals between trays. The cells may make up part of a tray of, *e.g.*, 10 x 10 cells spaced, *e.g.*, 0.5 cm apart. Each tray could be 18 x 18 cm, extra space may be provided at the edges of the tray for fiducial holes. Each tray may have a series of fiducial holes along the outer edge of the tray.

The invention may also be used with a separate device to place the first subunit in each cell. If N were 10, for example, then this separate device would consist of 10 columns, each with a capacity of 100 cc. The columns could be roughly 10 cm high and $10^{0.5}$ cm, *i.e.*, 3.6 cm in diameter.

The first subunit would be contained in each column. For example, subunit A in column 1, and subunit B in column 2, and so on. This is a first step library and can be used for other purposes. The contents of each column may be added to one tray, filling all the cells. A in one tray, B in another tray, and so on.

The trays may be stacked on top of each other, starting with a "base" and finishing with a "lid," threading the guides through the fiducial holes of each tray, and seating each tray into the tray below. The trays may then be assembled together so that a cube approximately 18 cm^3 is assembled.

The base tray may contain conduits for the removal of waste. The top tray, or lid, may contain the conduits for the entry of reagents. Reagents may be driven through the conduits by any suitable means, including gravitational, pressure differential, mechanical or electromagnetic. The trays may be made by machining successive sheets of plastic and then bonding them together. However, other

suitable materials such as metal, glass or composites could be utilized. When bonded together, the trays may direct the fluid from column 1 of cells to a common outlet.

For example the lid may contain conduits and entry ports to allow the addition of reagents: it may have the conduit built in. The conduits of the top tray may have a series of holes. The conduit allows the addition of A to the first row, B to the second, C to the third and so on. The holes allow the second member of the library compositions to be added to each row of stacked cells.

To complete the synthesis one may either (a) remove the lid, rotate it through 90 degrees and replace it, or (b) position a second conduit at right angles to the first and slightly offset so that the holes exiting the second can go straight through the first without interfering with it.

The device may be dismantled as follows:
Each tray may be put in a device that allowed the release of each reactant and collection of each reactant into a tray with, *e.g.*, glass vials. These could then be lyophilized, capped and held as stock.

If linear dimensions are scaled by $C^{1/3}$, capacity increases by C. A machine making 27 times the amount, *i.e.*, a gram of each compound would only be about 50 cm cubed, or 20 inches on the side. If a two-fold volume excess of each reagent was used in each step then a 10^3 cubic stack would require 2 liters in each pass.

The entire cube could also be inverted or shaken, provided enough space is left inside each cell.

The filling of the cell could also be automated (as in a fraction collector) and the other functions of the device could also be automated.

<u>Isolating the Compounds of the Synthesized Library</u>

Compounds in the combinatorial library synthesized by the present invention may be purified by any of the

techniques well known in the art. These techniques include, but are not limited to, precipitation, thin layer chromatography, column chromatography, high pressure liquid chromatography, crystallization, gel electrophoresis, and filtration.

Screening the Synthesized Library

A combinatorial library synthesized by the three-dimensional conduit synthesis of the present invention may be screened by any method well known in the art. These methods include, but are not limited to, ELIZA plating, receptor binding, southern, western and northern blotting, and competitive binding.

One method utilizing this approach that may be pursued in the isolation of such receptor-binding molecules would include the attachment of a combinatorial library molecule, or a portion thereof, to a solid matrix, such as agarose or plastic beads, microtiter wells, petri dishes, or membranes composed of, for example, nylon or nitrocellulose, and the subsequent incubation of the attached combinatorial library molecule in the presence of a potential combinatorial library molecule-binding compound or compounds. Attachment to said solid support may be direct or by means of a combinatorial-library-compound-specific antibody bound directly to the solid support. After incubation, unbound compounds are washed away, component-bound compounds are recovered. By utilizing this procedure, large numbers of types of molecules may be simultaneously screened for receptor-binding activity.

Administration of the Featured Compounds

After a promising compound has been identified by a screening method, the identified compound can be administered to a patient alone, or in a pharmaceutical composition comprising the identified active compound and a carrier or excipient. The compounds can be prepared as pharmaceutically acceptable salts (i.e., non-toxic salts

which do not prevent the compound from exerting its effect).

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical preparations for oral use can be obtained, for example, by combining the active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free base form of the compound is first dissolved in a suitable solvent such as an aqueous or aqueous-alcohol solution, containing the appropriate acid. The salt is then isolated by evaporating the solution. In another example, the salt is prepared by reacting the free base and acid in an organic solvent.

Carriers or excipient can be used to facilitate administration of the compound, for example, to increase the solubility of the compound. Examples of carriers and excipients include calcium carbonate, calcium phosphate, various sugars or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. The compounds or pharmaceutical composition can be administered by different routes including intravenously, intraperitoneally, subcutaneously, and intramuscularly; orally, topically, or transmucosally.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers, such as physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as

appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Agents intended to be administered intracellularly may be administered using techniques well known to those of ordinary skill in the art. For example, such agents may be encapsulated into liposomes, then administered as described above. Liposomes are spherical lipid bilayers with aqueous interiors. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external microenvironment and, because liposomes fuse with cell membranes, are efficiently delivered into the cell cytoplasm.

All patents and publications mentioned in this specification are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication is specifically and individually indicated to be incorporated by reference.

It will be readily apparent to one skilled in the art that various substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

Claims

1. A multidimensional conduit device for molecular synthesis comprising:

(a) a first array of cells aligned along one or more axes;

(b) at least a second array of cells aligned along one or more axes; and

(c) means for communication among said first and second arrays of cells and to and from each cell in said arrays of cells; and

(d) means for moving substrates and reagents among said means for communication.

2. The device of claim 1, wherein said cells of said first array are planarly arranged.

3. The device of claim 1, wherein said second array of cells are planarly arranged.

4. The device of claim 1, wherein said second array of cells is in a plane that is partially offset from the plane in which said first array of cells is located.

5. The device of claim 1, further comprising N arrays of cells.

6. The device of claim 5, wherein any one of the arrays of said N arrays of cells in a plane is offset from any other array of said N arrays of cells.

7. The device of claim 5, wherein at least one of the N arrays is rotatable about an axis perpendicular to said N arrays.

8. The device of claim 1, wherein said means for communication comprise conduits among said arrays.

9. The device of claim 1, wherein said means for moving substrates and reagents to and from each cell in said array of cells comprise gravitational force.

10. The device of claim 1, wherein said means for moving substrates and reagents to and from each cell in said array of cells comprise a pressure differential.

11. The device of claim 1, wherein said means for moving substrates and reagents to and from each cell in said array of cells comprise an electromagnetic force.

12. The device of claim 1, wherein said means for moving substrates and reagents to and from each cell in said array of cells comprise a mechanical force.

13. The device of claim 1, wherein each cell of said array of cells comprises a porous base having holes ranging in diameter from 1 micron to 1000 microns.

14. The device of claim 1, wherein each cell of said array of cells comprises a porous base having holes ranging in diameter from 10 microns to 500 microns.

15. The device of claim 1, wherein each cell of said array of cells comprises a porous base having holes ranging in diameter from 25 microns to 200 microns.

16. The device of claim 1, wherein each cell of said array of cells comprises a porous base having holes ranging in diameter from 50 microns to 100 microns.

17. A multidimensional conduit device for molecular synthesis comprising:

(a) cells arranged in a planar element, wherein each cell has a porous base, further wherein said planar elements are vertically stackable;

(b) first conduits connecting cells within a single planar element;

(c) second conduits connecting cells among said planar elements; and

(d) means for driving reagents through said first and second conduits.

18. A method for multidimensional conduit synthesis comprising the steps of:

(a) adding substrate to beads;

(b) positioning said beads into stackable porous based cells arranged in stacked trays;

(c) adding and evacuating reagents from said stacked.

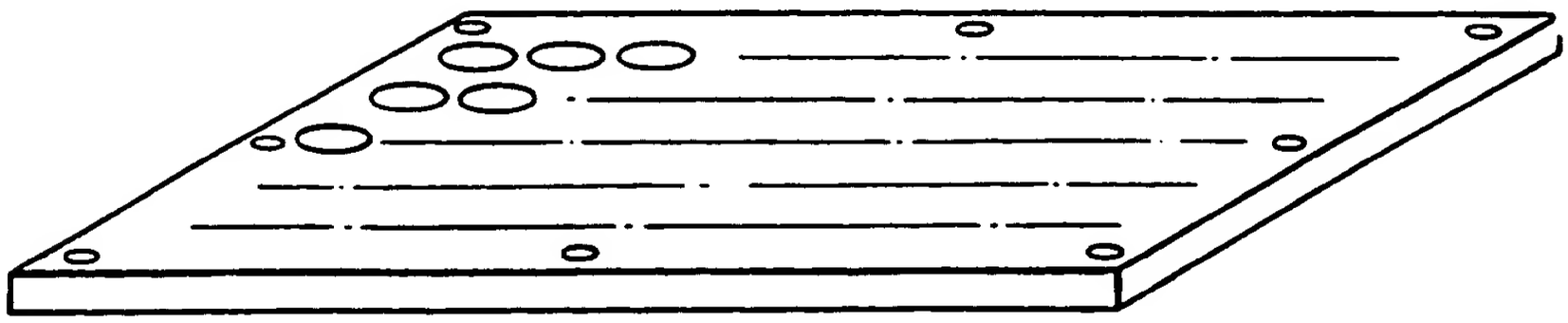

Fig. 1

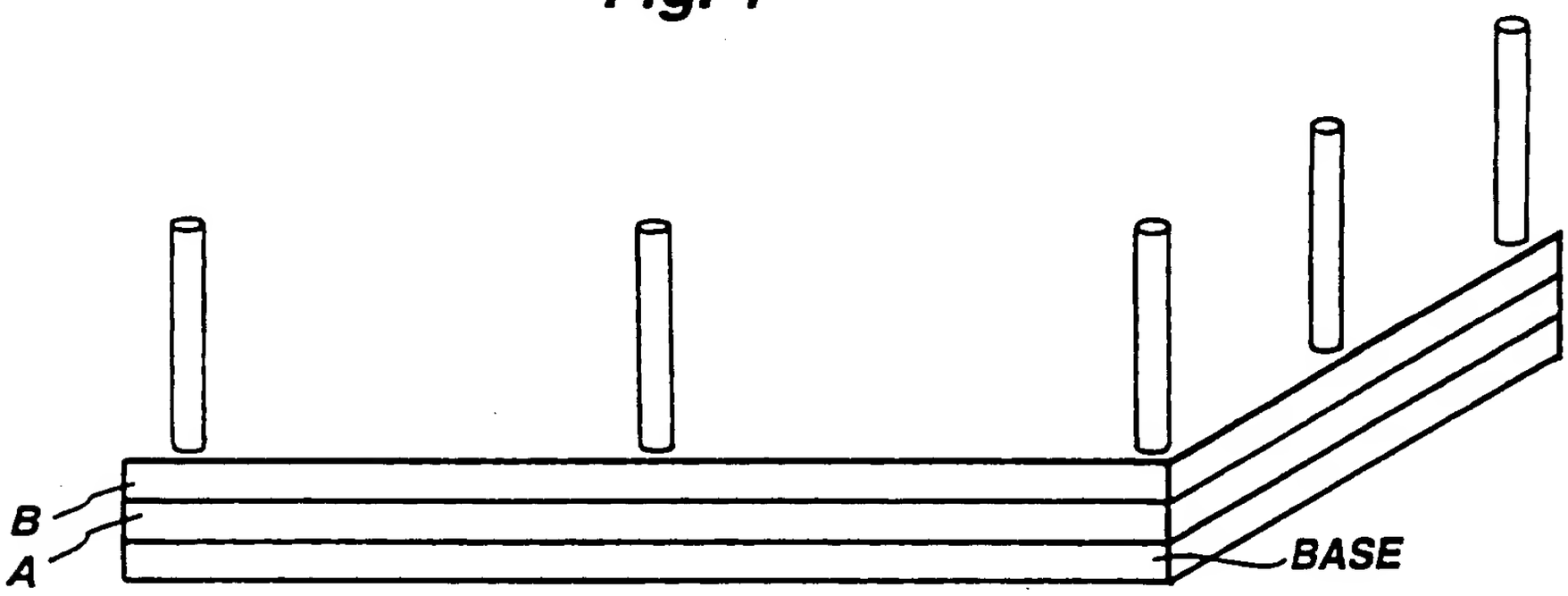

Fig. 2

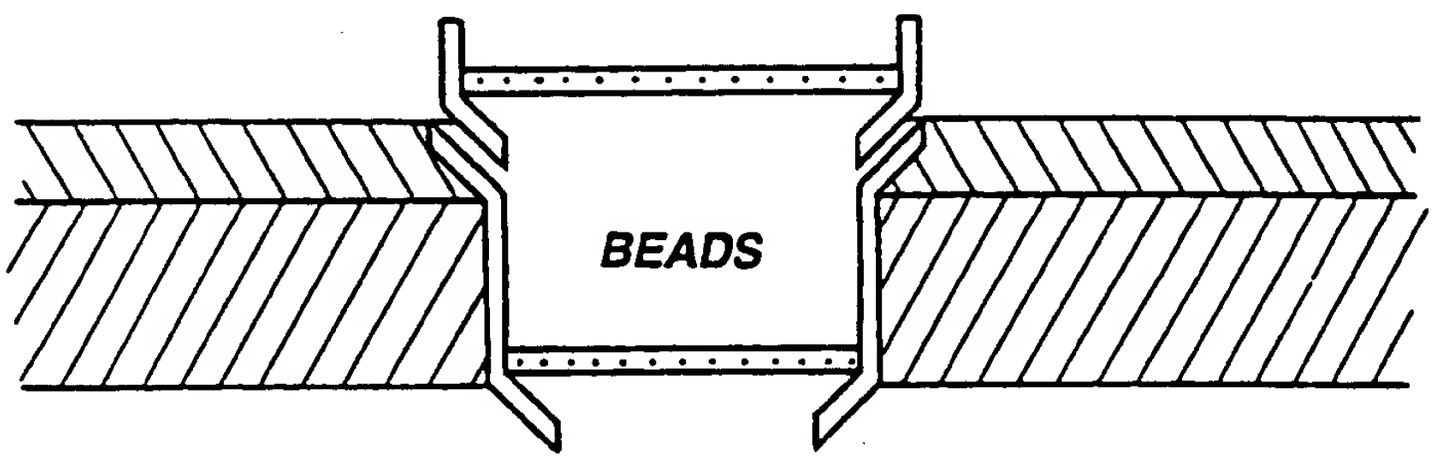

Fig. 3A

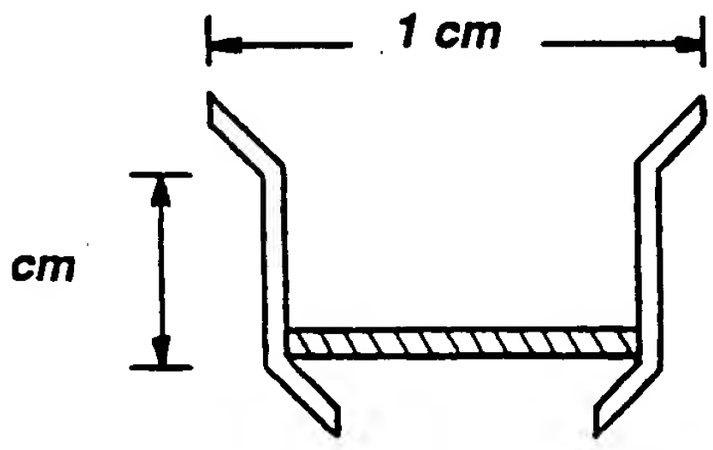

Fig. 3B

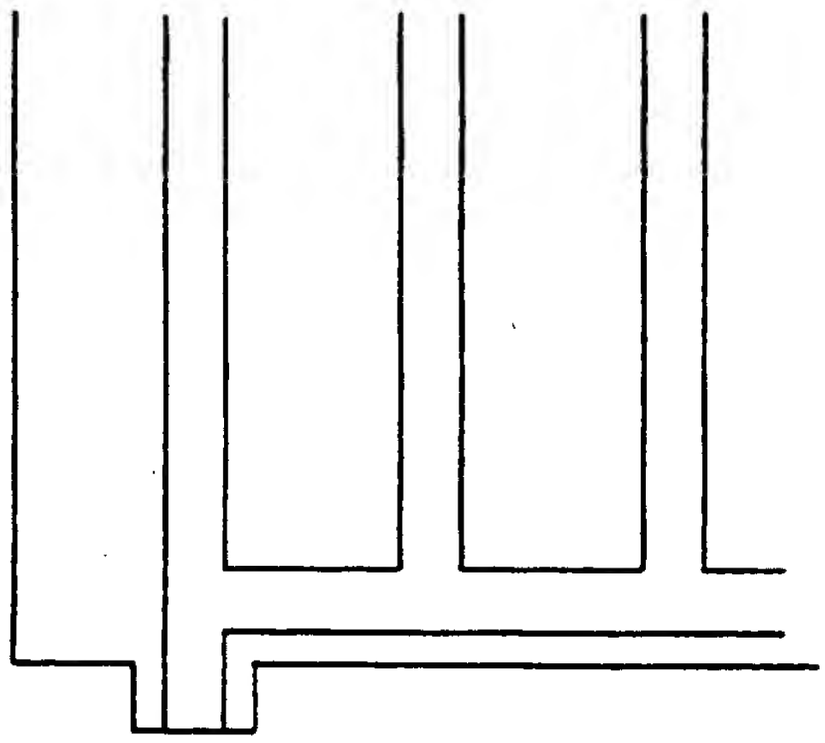

Fig. 4A

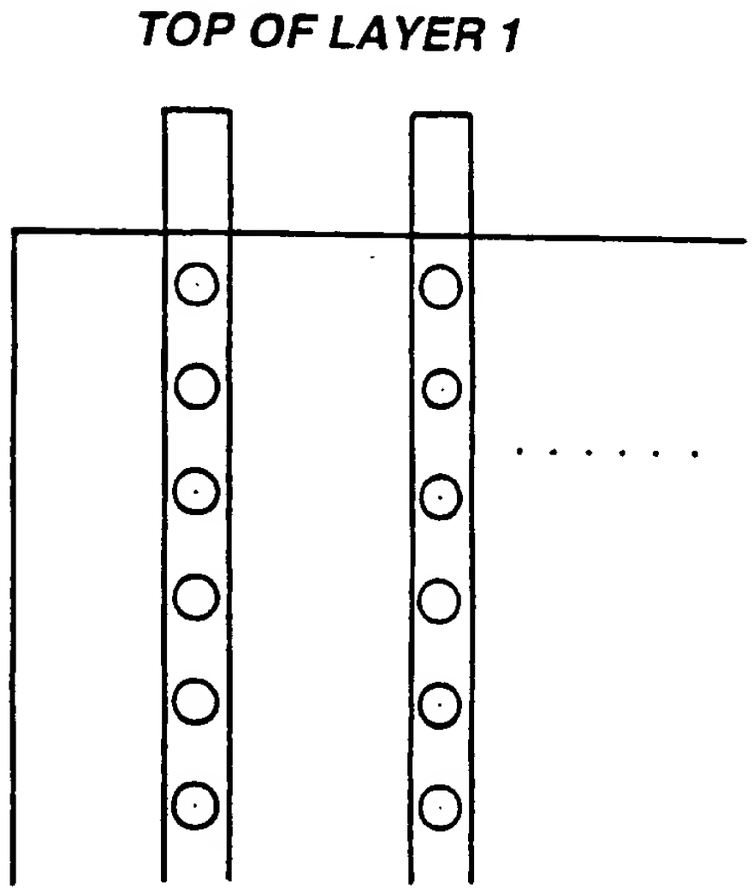

Fig. 5A

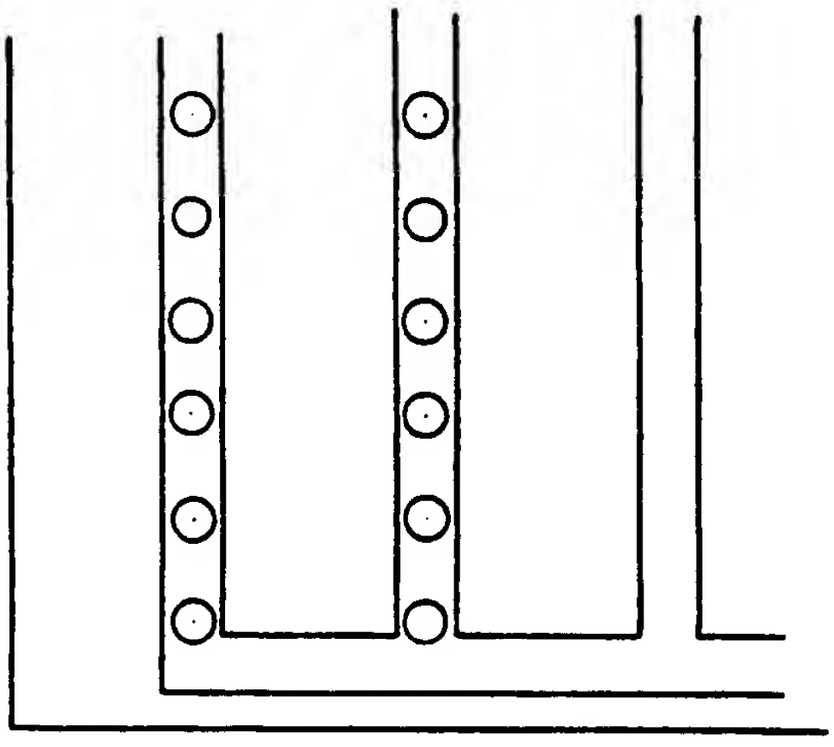

Fig. 4B

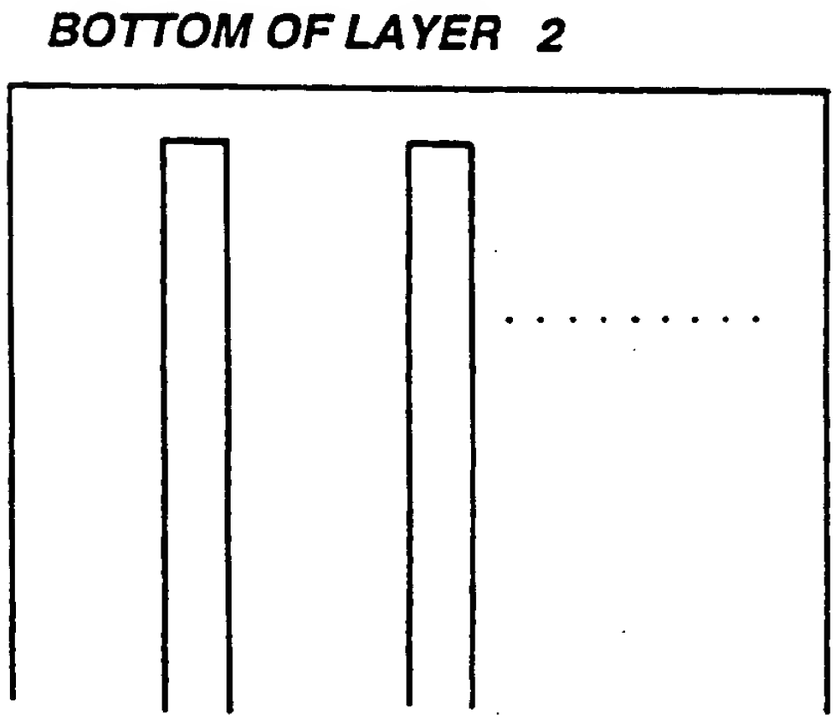

Fig. 5B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 95/00626

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01L3/00 B01J19/00 C07K1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01L B01J C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,89 10188 (EUROPEISCHES LABORATORIUM FÜR MOLEKULAR BIOLOGIE) 2 November 1989 see page 7, line 10 - line 33 see page 8, line 10 - line 26 see page 9, line 25 - page 10, line 5 ---	1
A	WO,A,94 05394 (ARRIS PHARMACEUTICAL CORPORATION) 17 March 1994 see page 11, line 4 - page 12, line 5 see page 14, line 18 - line 24; figure 3 see page 20, line 5 - page 21, line 3; figures 1-3 --- -/--	1,17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 November 1995	22.11.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Hocquet, A

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INTERNATIONAL SEARCH REPORT

Inter[illegible]nal Application No
PCT/IB 95/00626

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A	GB,A,2 158 075 (HAMMIL) 6 November 1985 see page 1, line 126 - page 2, line 42; figures 1,2,4	1,17,18

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